Antigenic Spectrum in Membranous Nephropathy: A Comprehensive Analysis of PLA2R, THSD7A, and NELL-1

Dear Editor,

Membranous nephropathy (MN) is an immune complex-mediated glomerular disease, typically presenting with nephrotic-range proteinuria and hypoalbuminemia. Recent understanding of MN pathogenesis has prompted a shift from traditional "primary" (idiopathic) to "secondary" (systemic) classification toward an antigen-based framework. In this revised scheme, cases with detectable autoantibodies against podocyte antigens—most commonly phospholipase A2 receptor (PLA2R), followed by Thrombospondin Type 1 Domain Containing 7A (THSD7A) and Neural Epidermal Growth Factor-Like 1 (NELL-1) are designated as antigen-associated MN. MN occurring in systemic conditions (e.g., lupus nephritis, malignancies, rheumatoid arthritis, or infections such as hepatitis C) is classified as systemic MN.

This ambispective observational study was conducted at a tertiary center in Sir Gangaram Hospital, New Delhi (retrospective: January 2018–March 2021; prospective: up to September 2022) on adults with biopsy-proven MN. Detailed methodology, inclusion/exclusion criteria, clinical evaluations, and antigen staining protocols have been provided in the Supplementary Methods.

Of 90 patients with biopsy-proven MN, 72 (80%) had antigen-associated MN and 18 (20%) had systemic MN. The mean age was 42.0 ± 14.6 years with a slight male predominance (1.19:1). Systemic MN was often linked to lupus nephritis (14/18, 78%), followed by malignancy (11%), rheumatoid arthritis (5.5%), and hepatitis C (5.5%), while 25 patients (27.8%) had hypothyroidism, 27 (30%) had hypertension, and 15 (16.7%) had diabetes mellitus. Mean serum creatinine at biopsy (1.2 ± 1.24 mg/dL, median 0.89) was significantly higher in antigen-associated MN (2.7 ± 1.3 mg/dL) than systemic MN (0.86 ± 0.49 mg/dL) (p=0.035). Clinical features have been described in Table 1. Regarding podocyte antigen staining, PLA2R was identified in 44 of 72 (61.1%) antigen-associated MN vs. 4 of 18 (22.2%) in systemic MN (p=0.004); THSD7A in 4 (5.6%) antigen-associated MN and none in systemic MN**;** NELL-1 in 8 of 72 (11.1%) antigen-associated MN and 1 of 18 (5.6%) systemic MN. Antigen-associated MN was frequently associated with PLA2R positivity and more proteinuria, whereas systemic MN primarily resulted from lupus nephritis. Table 1 summarizes the number of patients and outcomes in each treatment group with a median follow-up of 15.4 (±2.1) months.

The distribution in this study was comparable to previous Indian studies.[1,2] Antigen-associated MN (n=72) occurred more frequently in older adults. Systemic MN occurred in younger patients, primarily driven by lupus nephritis. There was a slight male predominance (M: F = 1.19). The diabetes mellitus prevalence (16.7%) was higher compared with Subramanian *et al*.[1] (8.3%) and Gopalakrishnan *et*

Table 1: Clinical features and treatment modalities and outcomes in MN patients

Parameter	Antigen-associated MN (n = 72)	Systemic MN (n = 18)	p value
Anemia	31 (43.1%)	9 (50.0%)	0.596
Oedema	69 (95.8%)	18 (100%)	1
Microscopic hematuria	21 (29.1%)	9 (50.0%)	0.103
Renal dysfunction	20 (27.8%)	3 (16.7%)	0.546
Hypercholesterolemia	51 (70.8%)	9 (50.0%)	0.94
Hypoalbuminemia	48 (66.7%)	9 (50.0%)	0.274
Nephrotic syndrome	42 (58.3%)	6 (33.3%)	0.057
Nephrotic range proteinuria	60 (83.3%)	13 (72.2%)	0.28
Mean serum creatinine (mg/dL)	2.7 ± 1.3	0.86 ± 0.49	0.035
Treatment modality, n	Response (CR+PR)	NR (n, %)	Relapse (n, % of responders)
Supportive care only, 12	5 (41.7%)	7 (58.3%)	0 (0%)
Steroids + cyclophosphamide, 31	24 (77.4%)	7 (22.6%)	4 (16.7%)
Calcineurin inhibitors, 7	7 (100%)	0 (0%)	1 (14.3%)
Rituximab, 24	19 (79.1%)	5 (20.8%)	2 (10.5%)
Mycophenolate + steroids, 12	11 (91.7%)	1 (8.3%)	2 (18.2%)
Lost to follow-up, 4	–	–	–

Complete remission (CR): UPCR <300 mg/g, Partial remission (PR): UPCR >300 mg/g but with >50% reduction from baseline. Non-response (NR): Patients who did not achieve CR or PR. MN: Membranous nephropathy.

al.[2] (5%). This discrepancy may reflect variations in biopsy practices and emphasizes cautiously evaluating nephrotic-range proteinuria in patients with diabetes mellitus to differentiate between antigen-associated MN and diabetic kidney disease.[3,4]

PLA2R was positive in 61.1% of antigen-associated MN, consistent with previously reported 50–80% prevalence rates. Among the remaining, a significant proportion were THSD7A (4.6%) and NELL-1 (11.1%) positive. Despite these findings, 60.7% of PLA2R-negative antigen-associated MN cases (17) remained undiagnosed for any of the three antigens (PLA2R, THSD7A, or NELL-1). These antigen-negative cases highlight the potential involvement of other rare or unidentified antigens requiring further exploration using advanced diagnostic tools. NELL-1 positivity (10%) was not associated with malignancy as reported in other studies.[3-6] The lack of malignancy association with both THSD7A and NELL-1 in this study may indicate regional or population-specific variations. No patients, including those with NELL-1-positive MN, reported using skin fairness creams or alternative medicines. Three patients (two PLA2R+THSD7A and one PLA2R+NELL-1) demonstrated dual staining, a rare overlap previously only documented in isolated reports.[S1-S3] Larger studies are needed to clarify whether dual-positive MN follows a unique disease trajectory.

Antigen-associated MN exhibited greater nephrotic-range proteinuria burden compared to systemic MN. Hypercholesterolemia and elevated serum creatinine levels were consistent with findings in earlier Indian studies,[1,2] though renal dysfunction was present in only a quarter of the cohort. Notably, serum creatinine was significantly higher in antigen-associated MN than systemic MN ($p=0.035$), underscoring more significant renal involvement in primary disease. PLA2R positivity correlated strongly with nephrotic syndrome and nephrotic-range proteinuria, similar to prior findings.[S4] Although THSD7A- and NELL-1-positive cases had severe proteinuria, small numbers prevented statistical significance. Larger registries are needed to delineate the prognostic implications of each antigen subtype.

A limitation is that immunostaining was confined to only three antigens: PLA2R, THSD7A, and NELL-1. Although novel antigens, such as EXT1/EXT2 and Semaphorin 3B, have been reported, their lower prevalence, absence of widely available reagents, and resource constraints limited the study to these three antigens.

In conclusion, antigen-associated MN constituted 80% of cases, predominantly linked to PLA2R, which correlated strongly with nephrotic-range proteinuria. Systemic MN was most often attributed to lupus nephritis. THSD7A and NELL-1 were less frequently identified, and dual positivity was rare. Overall, these findings emphasize the value of antigen-specific testing in refining MN classification and guiding individualized treatment approaches.

Conflicts of interest: There are no conflicts of interest.

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How to cite this article: Jain A, Tiwari V, Gupta A, Gupta P, Deb R, Bhargava V, *et al.* Antigenic Spectrum in Membranous Nephropathy: A Comprehensive Analysis of PLA2R, THSD7A, and NELL-1. Indian J Nephrol. doi: 10.25259/IJN_72_2025

Received: 02-02-2025; **Accepted:** 23-02-2025; **Online First:** 17-04-2025; **Published:** ***

DOI: 10.25259/IJN_72_2025

Supplementary available at: https://dx.doi.org/10.25259/IJN_72_2025